AD________________

Award Number: DAMD17-98-1-8218

TITLE: Obesity, Hormone Receptor Status, and Breast Cancer Occurrence and Survival in New Mexico Hispanic and Non-Hispanic White Women

PRINCIPAL INVESTIGATOR: Diane Crumley, Ph.D.

CONTRACTING ORGANIZATION: University of New Mexico Health Sciences Center
Albuquerque, New Mexico 87131

REPORT DATE: October 2001

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)

2. REPORT DATE
October 2001

3. REPORT TYPE AND DATES COVERED
Annual Summary (1 Oct 00 - 30 Sep 01)

4. TITLE AND SUBTITLE
Obesity, Hormone Receptor Status, and Breast Cancer Occurrence and Survival in New Mexico Hispanic and Non-Hispanic White Women

5. FUNDING NUMBERS
DAMD17-98-1-8218

6. AUTHOR(S)
Diane Crumley, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of New Mexico Health Sciences Center
Albuquerque, New Mexico 87131

E-Mail: crumley@mail.unm.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Report contains color

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Over the past 30 years, breast cancer incidence rates among Hispanic women in New Mexico have doubled, and mortality rates have increased over 50%. The factors responsible for these trends are not currently understood. This post-doctoral training project was designed to investigate whether ethnic differences in body composition and tumor hormone receptor status contribute to differences in breast cancer survival among New Mexico women. Analyses completed in Year 2 utilized data from 1484 breast cancer cases from three population-based breast cancer cohorts in New Mexico. Results indicate that Hispanics experienced higher 5-yr. all-cause and breast cancer mortality, compared to non-Hispanic white women (NHW). Breast cancer and all-cause mortality was not significantly associated with body mass index (BMI) when all three study cohorts were combined. Within the Prognosis Study cohort (n=650, 1996-99), total body fat and peripheral obesity measures were associated with negative estrogen receptor status among Hispanic patients only. In turn, estrogen receptor negative status was associated with increased breast recurrence rates and mortality. Tumor size was significantly associated with measures of centralized obesity among NHW patients only. Future research will continue to investigate factors associated with the ethnic differences observed in the relationships between body composition and breast cancer prognosis.

14. SUBJECT TERMS
Breast Cancer, obesity, Hispanics, epidemiology

15. NUMBER OF PAGES
33

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION

Background

Over the past 30 years, breast cancer incidence rates among Hispanic women in New Mexico have doubled, and mortality rates have increased over 50%. The factors responsible for these trends are not currently understood. Also alarming , are the results of a study examining ethnic differences in survival through time among members of a large HMO in New Mexico, which included Hispanic, Native American and non-Hispanic white (NHW) breast cancer patients. They found improvement in breast cancer survival between 1983 and 1992 for Native American and NHW women, but observed no improvement among Hispanic women, even after adjusting for extent of disease at diagnosis and treatment. This post-doctoral training project was designed to contribute to the understanding of the factors responsible for the lack of improvement observed among New Mexico Hispanic breast cancer patients.

Obesity has been shown to increase the risk of developing postmenopausal breast cancer, and has been associated with poorer outcomes after diagnosis in several studies. A large national study has estimated that 47% of Hispanic women and 32% of NHW women are overweight (greater than 20% above ideal weight for height). The impact of increasing obesity on breast cancer rates and mortality has not been thoroughly examined. The goals of the post-doctoral training project as stated in the original proposal are: (1) to investigate the relationships between measures of body composition and breast cancer risk in Hispanic and NHW new Mexico women; (2) to investigate the relationships between body composition, hormone receptor status and prognosis; (3) to determine whether ethnic differences in obesity, central fat patterning, and the distribution of positive and negative estrogen receptor status contributes to differences in survival.

The proposed research has utilized existing data from two state-wide breast cancer case-control studies of breast cancer risk factors [the CDC's Cancer and Steroid Hormone Study (CASH) 1980-82 and the New Mexico Women's Health Study (NMWHS) 1992-94] and one cohort study (referred to as the Prognosis cohort) conducted in collaboration with the New Mexico Tumor Registry and the National Cancer Institute.

Review of Research Accomplished during Year One

During Year One of this training grant, analytic data-sets for the 633 cases with complete information on reported body mass index (BMI) and receptor status in the CASH and NMWHS were compiled, and 5-year survival after breast cancer diagnosis (all-cause mortality) was calculated and compared by ethnic group using Kaplan-Meier survival analysis. Relative 5-year survival was also calculated utilizing 1980 U.S. Life Tables that were gender, age, and ethnic specific. When 5-year survival following breast cancer diagnosis was compared by ethnicity *within* studies (CASH and NMWHS separately, there were no significant ethnic differences. However, when survival was compared *across* studies, NHW women in the 1992-94 NMWHS had significantly improved relative to NHW cases in the 1980-82 CASH study ($p<0.006$). In contrast, 5-year relative survival for Hispanic women in these two study cohorts did not show a significant improvement.

These analyses demonstrated that high BMI was significantly associated with increased all-cause mortality for NHW but not Hispanic breast cancer patients. Survival was significantly improved among NHW women with ER+/PR+ receptor status, but this trend was reduced and did not reach statistical significance for Hispanic women. The conclusion derived from these preliminary analyses of the first two study cohorts (diagnosed in 1980-82 and 1992-94) was that the factors associated with reduced survival among NHW women, were not significant factors predicting breast cancer outcome among Hispanic women. These preliminary results were presented in a platform presentation at the Era of Hope DOD Breast Cancer Research Program meeting in Atlanta, GA in June 2000.

RESEARCH ACCOMPLISHED: YEAR TWO

During Year Two of this training grant, the data from the 1996 - 1999 Prognosis study became available for editing, verification and for merging with the other two study data sets. The Prognosis Study is part of a multi-center study (called HEAL) funded by the National Cancer Institute to investigate the role of weight history, body composition, diet, exercise and hormones on breast cancer prognosis. In New Mexico, our cohort consists of 650 incident breast cancer cases that have completed interviews, body composition assessments and blood draws for endogenous hormones.

Results from the 1996-1999 Prognosis cohort

In contrast to the lack of ethnic difference in all-cause mortality observed in the earlier CASH and NMWHS cohorts, the more recent Prognosis cohort had significant ethnic differences in all-cause mortality ($p<0.012$). This was somewhat unexpected given that the proportion of Hispanic women diagnosed with more advanced regional disease has actually decreased across the 3 study cohorts (CASH 40%, NMWHS 36% and Prognosis cohort 22% see Appendix page 8). When this pattern was examined more closely, we found no ethnic difference in 5-year breast cancer survival for women diagnosed with local stage disease, but significant differences for regional disease (85% NHW vs. 76% for Hispanics). These results for the Prognosis cohort alone should be viewed as preliminary since mean 5 yr. follow-up for their cohort is currently 34.6 months, whereas mean 5 yr. follow-up for the CASH and NMWHS are 53.7 and 55.8 months respectively. To accommodate the differences in follow-up time for the three cohorts, 2.5-year survival was also calculated and presented in Table 1 below.

Survival results for the combined cohorts

There were 1484 cases utilized in the combined 5-year analysis of all-cause and breast cancer mortality. Hispanic women have reduced survivorship in both comparisons (all cause $p<0.035$, breast cancer only $p<0.002$ see Appendix pg. 8 for survival curves). Breast cancer and all-cause mortality was not significantly associated with BMI, when the three cohorts were combined. Women diagnosed with ER-/PR- tumors experience significantly higher breast cancer mortality compared to cases with ER+/PR+ tumors. The magnitude of this mortality difference was greater among Hispanics (NHW ER-/PR- had 16% mortality, compared to 21% mortality for ER-/PR- Hispanic women, refer to Appendix pg. 10 for curves). These results are summarized in Table 1 below.

Table 1. Ethnic comparisons of 2.5 and 5.0 year breast cancer survival by stage at diagnosis and hormone receptor status.

	NHW		Hispanic		
	% Survival	95% CI	% Survival	95% CI	p-value
Stage at Diagnosis					
2.5 Year Follow-up					
Local	97.5	(96.2, 98.9)	96.3	(94.1, 98.6)	
Regional	92.0	(88.1, 95.9)	88.7	(83.8, 93.6)	
5.0 Year Follow-up					
Local	93.3	(90.8, 95.9)	91.7	(88.1, 95.2)	
Regional	84.8	(79.2, 90.5)	75.9	(68.9, 82.8)	*0.019
ER/PR Status					
2.5 Year Follow-up					
ER+/PR+	97.5	(95.9, 99.0)	97.1	(94.8, 99.4)	
ER-/PR-	91.5	(86.6, 96.3)	90.7	(85.5, 96.0)	
ER/PR Status					
5.0 Year Follow-up					
ER+/PR+	94.8	(92.3, 97.3)	91.8	(87.8, 95.8)	
ER-/PR-	84.3	(77.3, 94.1)	78.6	(70.8, 86.5)	
		**0.005		**0.003	
Combined Cohorts					
2.5 Years	96.5	(95.3 97.7)	93.5	(91.3, 95.6)	
5.0 Years	91.9	(89.8, 94.0)	86.2	(83.0, 89.3)	*0.002

*refers to significant ethnic differences in 5-yr. survival for regional disease, and all stages combined.
** refers to significant 5-yr. survival differences by ER/PR status for both ethnicities.

Recurrence and Mortality: Data from the Prognosis cohort

Of the 43 deceased participants, (diagnosed in 1996-1999) we currently have cause of death information for 35 women. Of these, 46% died of causes other than breast cancer (19% were Hispanic, 81% were non-Hispanic white). Death due to breast cancer accounted for 54% of the overall deaths (47% were Hispanic, 53% were NHW). Given that the ethnic distribution in the entire cohort is approximately 24% Hispanic and 76% NHW, it can be seen that a larger than expected proportion of Hispanic women died from breast cancer.

With respect to self-reported recurrence information obtained during the 24 month Follow-up interview, 22 participants have reported recurrence to date. 73% of the recurrence cases are currently alive and 27% are deceased. Of the recurrences, 41% are Hispanic and 59% are NHW. Similar to the ethnic distribution of death from breast cancer, Hispanic women show higher than expected recurrence rates.

A preliminary description and comparison of factors associated with recurrence and/or death due to breast cancer is included in Table 2. Stage at diagnosis, Hispanic ethnicity, negative estrogen receptor status, and longer mammography screening intervals were all significantly associated with recurrence/death from breast cancer. Menopausal status, family history, and BMI at diagnosis did not show significant associations. When ethnicity was examined further, Hispanic women were more likely to be among the recurrences/deaths for all stages of disease, however the ethnic differences were particularly significant among women diagnosed with TNM stages IIA and IIB. For example, among 107 women diagnosed with stage IIA, approximately 4% of NHW women later experienced recurrence/death during follow-up vs. 18.5 % of the Hispanic Stage IIA cases. This preliminary description demonstrates the need for continued follow-up in order to facilitate a more in-depth analysis of the factors contributing to the poorer outcomes observed to date among Hispanic breast cancer cases in this study cohort.

Table 2. Factors associated with self-reported recurrence and/or death from breast cancer

	No Recurrence		Recurrence and/or Death Breast Cancer		p-value
	N	%	N	%	
All:	446		35		
TNM stage:					
0	88	19.7	3	8.6	0.0003
I	221	49.6	13	37.1	
IIA	98	22.0	8	22.9	
IIB	32	7.2	10	28.6	
IIIA IIIB	5	1.1	1	2.9	
Ethnic group:					
Non-Hispanic white	353	79.1	20	57.1	0.0023
Hispanic	93	20.9	15	42.9	
Menopausal status:					
Post-	324	72.6	24	68.6	0.5961
Pre-	122	27.4	11	31.4	
Estrogen-receptor status:					
Not done/unknown	129	28.9	11	31.4	0.0078
Positive	256	57.4	14	40.0	
Negative/Borderline	61	13.7	10	28.6	
BMI at DX (measured)					
< 25	198	44.4	15	42.9	0.8863
25+	223	50.0	16	45.7	

Analysis of Body Composition, ER- status and Tumor Size: the Prognosis cohort

It can be seen in Table 2 that Hispanic ethnicity, stage at diagnosis, and ER negative (ER-) status are all significantly associated with recurrence or death from breast cancer. There have been several studies that show that Black and Hispanic women are more likely to be diagnosed with ER negative tumors, and that since these tumors don't typically respond to anti-estrogen therapy, they are more difficult to treat and result in poorer survival. Understanding factors associated with the development of ER negative breast cancer could contribute to the development of prevention strategies that could particularly benefit these minority women.

The following analysis included Prognosis cohort participants with invasive disease, complete body composition measures including BMI, percent body fat and anthropometry, and known values for ER receptor status (yielding 353 women for inclusion, 84 Hispanic and 269 NHW). Among Hispanic women only, ER negative status was significantly related to high levels of total body fat, and measures of peripheral obesity including triceps and mid-thigh circumferences. This multiple logistic model adjusted for menopausal status, family history, age at first birth and mammography screening interval (refer to Appendix pg. 12 for details).

A similar model was produced that examined the above mentioned body composition measures in conjunction with tumor diameter. Among NHW women only, log tumor size was positively associated with increases in BMI and measures of centralized obesity including waist circumference and subscapular skinfolds (refer to Appendix pg. 12 for more detail). Although not quite reaching statistical significance among Hispanic women, tumor size was *negatively* associated with BMI at a magnitude similar to, yet *opposite* to what was observed among NHW women. Though preliminary, this is an interesting finding, and could imply one or both of the following: 1) Hispanic women with high BMI levels have different hormonal profiles than equally heavy NHW women; 2) factors that contribute to tumor growth differ by ethnicity. During the upcoming final year of this post-doctoral training grant, I plan to pursue this investigation in the Prognosis cohort to examine whether there are: 1) ethnic differences in the hormonal profiles associated with obesity, and 2) whether there are ethnic differences in hormonal profiles associated with ER negative vs. ER positive breast cancer tumors.

The role of physical activity and breast cancer risk: an analysis using the New Mexico Womens' Health Study (NMWHS) 1992-1994 case-control data

Since writing the proposal for this training grant, there have been a growing number of investigations that are examining the relationship between physical activity levels and the risk of breast cancer. Physical activity is hypothesized to reduce breast cancer risk through the following mechanisms: changes in fat distribution, alteration in sex hormone levels, reductions in metabolic and growth hormones, and modulation of immune function. Given the fact that low levels of physical activity are often associated with obesity, my faculty mentor, Frank Gilliland, MD. PhD. and I decided to investigate the roles of body mass index (BMI), diet and physical activity on breast cancer risk among the participants of the NMWHS, to more thoroughly examine the role of obesity and breast cancer risk.

In-person interviews provided data on self-reported usual and current body mass index (BMI), diet, and participation in leisure-time sport and recreational activity. Activity type and weekly duration were used to calculate weekly totals of metabolic equivalent hours (MET-hrs) of total and vigorous (>5 METs) energy expenditure. Vigorous physical activity was associated with reductions in breast cancer risk among both Hispanic and NHW women. The effects of physical activity appeared to be independent from reproductive factors, total energy intake and usual BMI. The overall protective effect of physical activity was larger in Hispanic women, mostly as a result of the larger protective effect seen in premenopausal Hispanics. The hypothesis proposed to explain this pattern is that physical activity preferentially reduces intra-abdominal fat stores that lead to a reduction in exposure to hormonal breast cell mitogens such as insulin and insulin-like growth factor. Premenopausal Hispanic women have a higher prevalence of centralized obesity than NHW women in New Mexico, so it is hypothesized that physical activity may exert a larger protective effect among Hispanic women. We were unable to test this hypothesis using the NMWHS population because there are no measures of body composition available. However, I plan to pursue this question in my final year of my training grant by utilizing the body composition, hormone and physical activity data that was collected from the participants of the Prognosis study. Please refer to the Appendix for a copy of our article on physical activity and breast cancer risk that was published this year in the American Journal of Epidemiology.

TRAINING ACCOMPLISHMENTS: YEAR 2

Continued Education:

"*Analysis of Epidemiologic Data: An Applied Approach , Epidemiology 743* ",
Graduate Summer Session in Epidemiology, July 23-27, 2001,
School of Public Health, Department of Epidemiology,
Univeristy of Michigan

"*Cancer Prevention, Epidemiology 751* ",
Graduate Summer Session in Epidemiology, July 23-27, 2001,
School of Public Health, Department of Epidemiology.
University of Michigan

"*Epidemiology Seminar, BioMed 604*"
Spring 2001 and Fall 2001
Masters in Public Health Program,
University of New Mexico, Health Sciences Center

KEY RESEARCH ACCOMPLISHMENTS: YEAR 2

--- Compiled analytic data-set for the Prognosis cohort study (n= 650) including editing, verifying and merging questionnaire, body composition, hormonal, and tissue characteristic data.

--- Performed Kaplan-Meier survival analyses of the effects of study cohort, BMI and estrogen/progesterone receptor status on all-cause and breast cancer mortality, by ethnicity for all three study cohorts combined (n=1484).

--- Using the more detailed data available for the 650 Prognosis cohort cases, examined the factors associated with recurrence and death from breast cancer (mean follow-up 34.6 months).

--- Conducted an analysis of the relationship between body composition measures, estrogen receptor status and tumor size among Hispanic and NHW Prognosis study participants.

--- Investigated the relationship between obesity, energy intake, physical activity and breast cancer risk utilizing the 1992-94 NMWHS case-control data-set.

REPORTABLE OUTCOMES: YEAR 2

--- **Published manuscript on the above mentioned physical activity and breast cancer risk analysis.**
Gilliland FD, Li YF, Baumgartner KB, Crumley DD, Samet JM. Physical Activity and Breast Cancer Risk in Hispanic and Non-Hispanic White Women. *American Journal of Epidemiology 2001;154:442-50.*
(Please refer to Appendix for copy of article)

--- **Invited lecture for presentation of breast cancer research funded by this training grant:**
October 9, 2001 "Body Composition, Tumor Characteristics, and Breast Cancer Prognosis among Hispanic and non-Hispanic New Mexico Women" University of New Mexico Masters in Public Health Program, *Epidemiology Seminar Series.* (Please refer to the Appendix for a copy of this presentation)

--- **Recommended for advancement from "Research Scientist III" staff position to "Research Assistant Professor",**
Dept. of Internal Medicine, University of New Mexico Scholl of Medicine (approval pending).

DEVIATIONS FROM ORIGINAL STATEMENT OF WORK

As was mentioned in my report last year, there has been a loss of three key faculty members in the Masters of Public Health Program at the University of New Mexico, where I had originally proposed to complete coursework. At the advice of my faculty mentor, I enrolled for classes last summer at the University of Michigan that were specifically geared toward my current research project. I plan to attend again next summer to take an additional four courses which will provide added scholastic background to my on-going breast cancer research experience. As described in the text of this report, I also plan to expand some of the original analyses proposed to include more in-depth investigations of the associations between body composition, ethnicity and breast cancer survival.

APPENDICES

1. **Copy of Invited Presentation for the University of New Mexico Epidemiology Lecture Series, Fall 2001**
2. **Reprint of published manuscript from American Journal of Epidemiology, 2001**

UNM Masters in Public Health Program

EPIDEMIOLOGY SEMINAR SERIES

Body Composition, Tumor Characteristics, and Breast Cancer Prognosis among Hispanic and non-Hispanic New Mexico Women

Guest Speaker:

Diane D. Crumley, Ph.D.
Epidemiology and Cancer Control Program
UNM School of Medicine

Learning Objectives:

1. To describe ethnic differences in breast cancer incidence and survival among non-Hispanic White and Hispanic New Mexico women.
2. To describe the relationships between body composition and hormone receptor status on breast cancer prognosis.
3. To examine ethnic differences in the associations between body composition measures and breast cancer prognosis.

Tuesday, October 9, 2001

Family Practice Center – Room 340

12:00 - 1:00 pm

(Feel free to bring your lunch)

This bi-weekly seminar series will be held on the 2nd and 4th Tuesdays from 12:00 – 1:00 pm in **Room 340** of the **Family Practice Center**. Individual lectures are **eligible for CME credit** (see below). The seminar is also offered as a 1 credit graduate course through the MPH Program. For more information please contact: Lorraine Halinka Malcoe, Ph.D.: 272-9471 or Lhmalcoe@salud.unm.edu .

The University of New Mexico School of Medicine, Office of Continuing Medical Education is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The Office of Continuing Medical Education designates this continuing medical education activity for a maximum of one (1) credit hour (per lecture) in Category 1 of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that s/he actually spends in the educational activity.

Target Audience: students, health researchers, physicians, physician assistants, nurses, midwives, nurse practitioners

Body Composition, Tumor Characteristics and Breast Cancer Prognosis among Hispanic and Non-Hispanic New Mexico Women

Diane D. Crumley, PhD
Epidemiology & Cancer Control Program
Fall, 2001

Introduction

- This presentation represents a summary of work completed during the first 2 years of my post-doctoral training grant
  - *awarded by the Dept. of Defense, Breast Cancer Research Program*
- The results presented today are preliminary, exploratory and descriptive

Acknowledgements

W. Curtis Hunt, Senior Biostatistician, EpiCC/NMTR

C. Key and D. Pathak, Principal Investigators
1980-82 *Cancer and Steroid Hormones (CASH) Study*

J. Samet, F.Gilliland, K. Baumgartner, Principal Investigators
1992-1994 *New Mexico Women's Health Study*

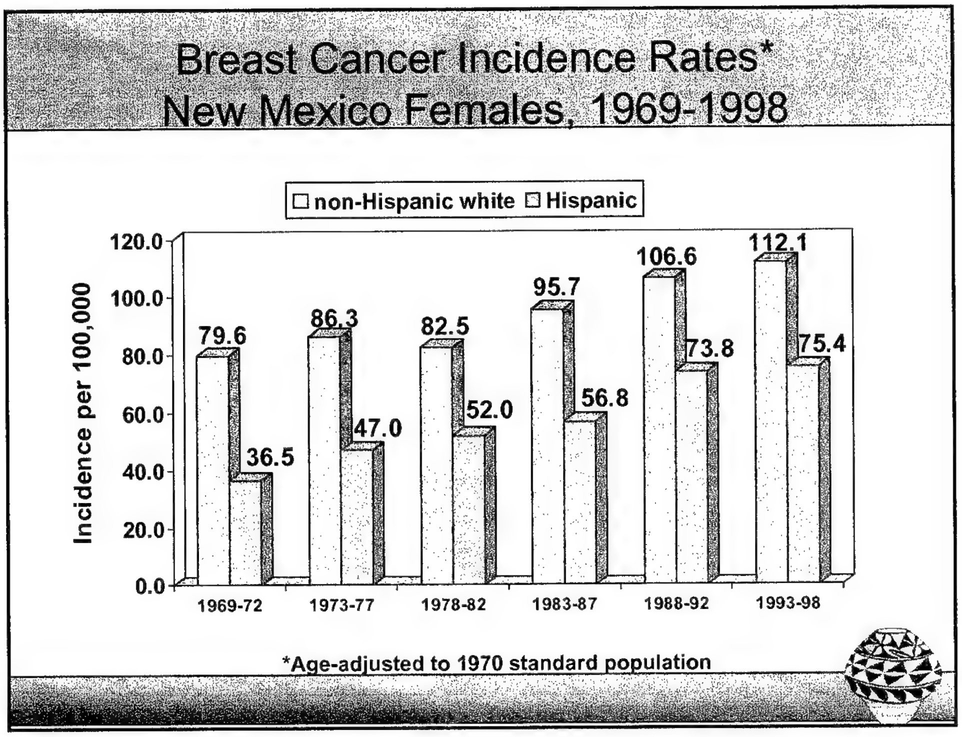
R. Baumgartner (PI) & K. Baumgartner (Co-PI) 1996-99 *Prognosis Study*

R. Rosenberg (Principal Investigator) and P. Stauber (Program Manager)
New Mexico Mammography Project

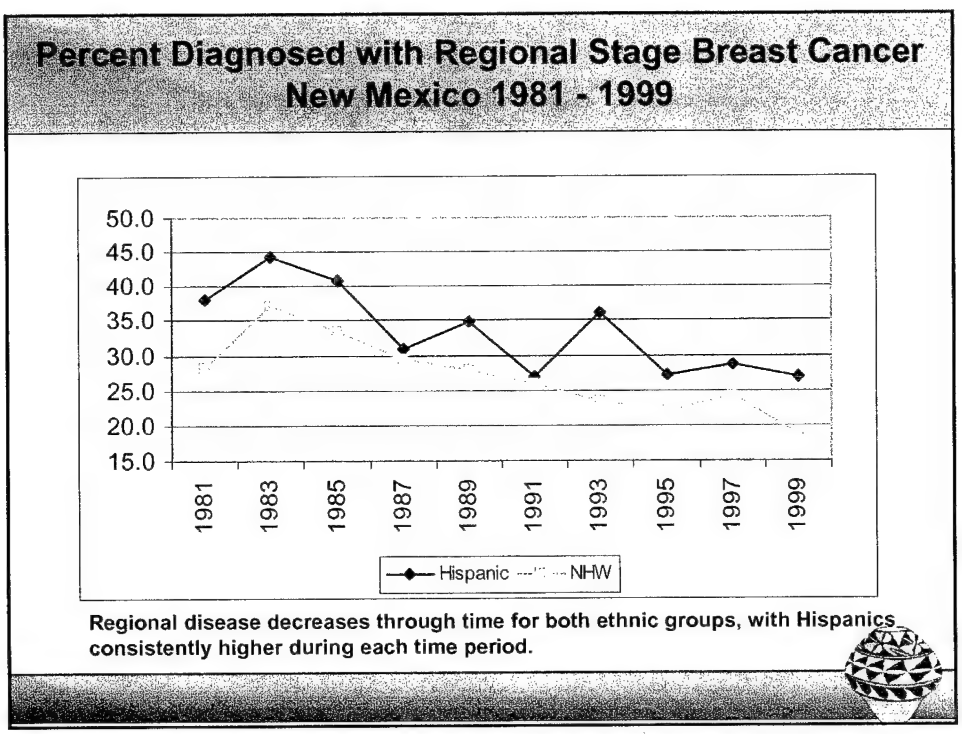
J. L. Bryant (Res. Coord.), K. Baca, P. James, C. Pankonin (Grad. Assist.)
Mammographic Density and Breast Cancer Prognosis Study

Outline of presentation

- An introduction to the research problem (ethnic differences in breast cancer survival)
- A brief review of the roles of body composition and hormone receptor status on prognosis
- Part I: Breast cancer survival by ethnicity, study cohort, body composition and ER/PR status
- Part II: Body composition measures and prognostic factors (ER status and tumor size)

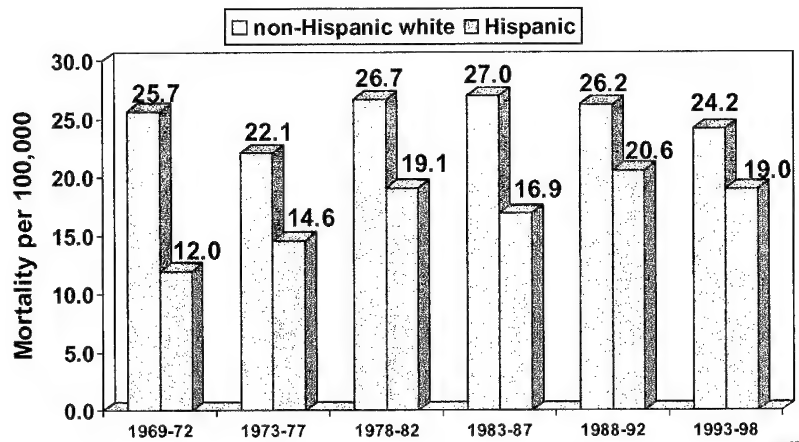


Breast Cancer Incidence Rates*
New Mexico Females, 1969-1998
non-Hispanic white
Hispanic
Incidence per 100,000
120.0
100.0
80.0
60.0
40.0
20.0
0.0
79.6
36.5
86.3
47.0
82.5
52.0
95.7
56.8
106.6
73.8
112.1
75.4
1969-72
1973-77
1978-82
1983-87
1988-92
1993-98
*Age-adjusted to 1970 standard population



Percent Diagnosed with Regional Stage Breast Cancer
New Mexico 1981 - 1999
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
Hispanic
NHW
Regional disease decreases through time for both ethnic groups, with Hispanics consistently higher during each time period.

Breast Cancer Mortality Rates*
New Mexico Females, 1969-1998



*Age-adjusted to 1970 standard population

NM Breast cancer mortality rates (continued)

- **To what extent do the observed differences in mortality patterns reflect ethnic differences in:**
  - Stage at diagnosis
  - Treatment

Frost et al. (1996) examined breast cancer survival among NHW, Hispanic and Native Americans diagnosed in New Mexico during 2 time periods (1973-82 and 1983-92).

After adjusting for stage at DX, and treatment received, Hispanic women had reduced survival (1983-92) compared to NHW, and did not experience improvements in relative 5 yr survival, in contrast to NHW and Na. Americans.

Ethnicity and Breast Cancer Prognosis: the role of obesity

Obesity at diagnosis has been shown to increase the risk of recurrence/or death from breast cancer.

In particular, centralized obesity is hypothesized to be associated with poor breast cancer outcome through the following mechanisms:

- elevated levels of bioavailable estrogens;
- higher insulin levels;
- subnormal levels of progesterone.

Hispanic women in New Mexico are more likely to exhibit centralized obesity, (and at younger ages), compared to NHW women.

Ethnicity and Breast Cancer Prognosis: the role of hormone receptor status

In normal breast tissue, estrogens are important regulators of cell growth and differentiation, and estrogen receptors are typically present at relatively low levels.

In contrast, approximately 70% of breast cancer tumors have relatively high levels of estrogen receptors (ER+).

Women with ER+ tumors can be treated with anti-estrogen therapies, and typically have improved survival; highly effective treatments for ER- tumors require more research.

Several studies have shown that Black (and perhaps Hispanic) women are more likely to develop rapidly growing ER- tumors.

Part I

An examination of breast cancer survival by:
- ethnicity
- study cohort
- Body Mass Index (BMI)
- ER/PR status

Objectives: Part I

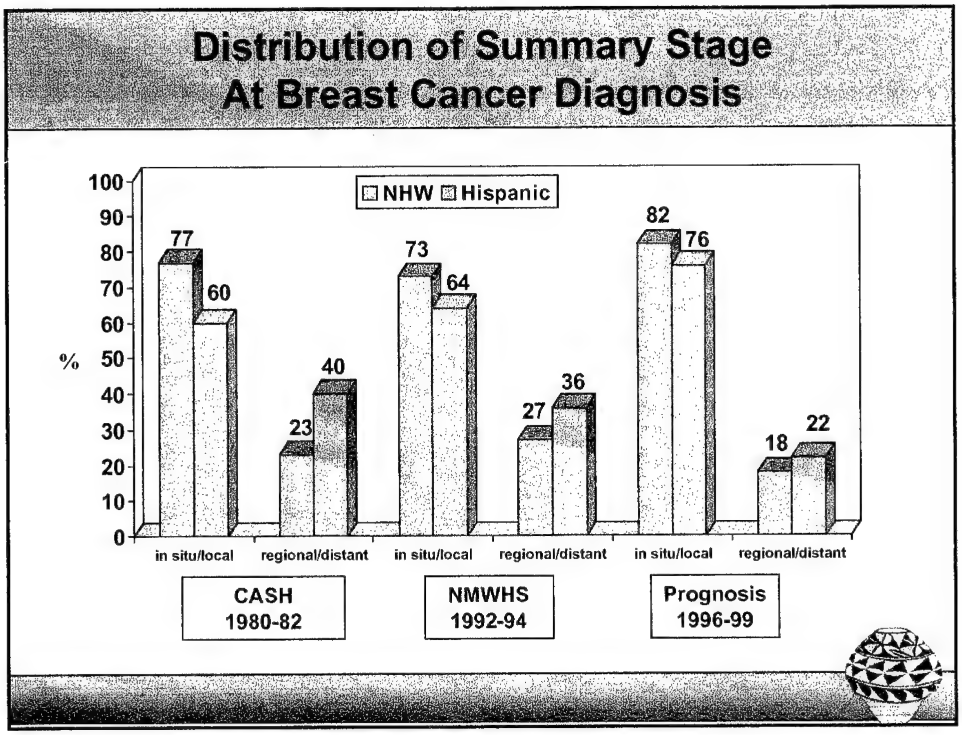
- To describe the effects of ethnicity,study cohort, body mass index (BMI) & hormone receptor status (ER/PR) on 5 year survival following breast cancer diagnosis
- To investigate whether there are ethnic differences in the relationships between obesity, receptor status, & breast cancer survival in Non-Hispanic white (NHW) & Hispanic New Mexico women

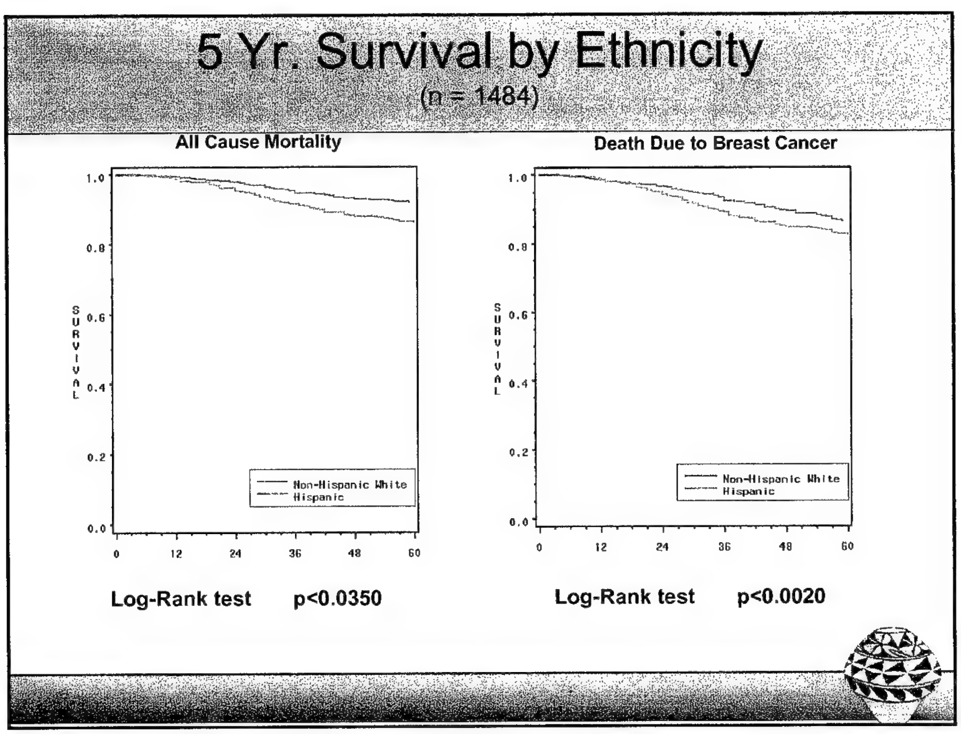
Study Cohorts

- 123 cases from the 1980-82 Cancer and Steroid Hormone Study (CASH)
  - a multi-center case-control study conducted by the CDC to examine breast cancer risk and hormonal exposure
- 711 cases from the 1992-94 New Mexico Women's Health Study (NMWHS)
  - a state-wide population-based case-control study of breast cancer risk factors
- 650 cases from the 1996-99 NMWHS Prognosis Study
  designed to investigate the role of body composition, diet, exercise and hormone on breast cancer prognosis

Descriptive Characteristics of the Study Cohorts

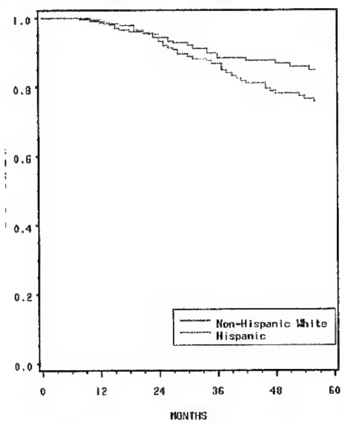
	CASH 1980-1982		NMWHS 1992-1994		Prognosis 1996-1999	
	NHW	Hispanic	NHW	Hispanic	NHW	Hispanic
	%	%	%	%	%	%
Menopause Status						
PRE	70.8	69.0	28.9	36.3	25.5	33.6
POST	29.2	31.0	71.1	63.7	74.5	66.4
Estrogen/Progesterone Receptor Status						
ER+PR+	44.7	38.9	56.6	53.5	70.7	53.5
ER-PR-	28.9	36.1	23.0	29.5	15.5	27.7
Unknown	41.5	37.9	22.4	18.1	31.5	33.6
Body Mass Index						
Low (BMI $\leq$21)	49.2	43.1	50.3	20.5	22.9	12.5
Mid (BMI 22-25)	33.8	29.3	36.6	42.3	30.7	26.3
High (BMI $\geq$26)	16.9	27.6	12.6	36.0	37.6	53.3
Unknown	-	-	.5	1.2	8.8	7.9


Distribution of Summary Stage
At Breast Cancer Diagnosis
NHW Hispanic
%
100
90
80
70
60
50
40
30
20
10
0
77
60
23
40
73
64
27
36
82
76
18
22
in situ/local
regional/distant
in situ/local
regional/distant
in situ/local
regional/distant
CASH
1980-82
NMWHS
1992-94
Prognosis
1996-99


5 Yr. Survival by Ethnicity
(n = 1484)
All Cause Mortality
Death Due to Breast Cancer
SURVIVAL
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
Non-Hispanic White
Hispanic
Log-Rank test p<0.0350
Log-Rank test p<0.0020

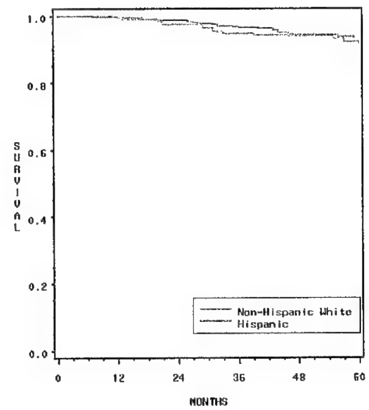
5 Year Breast Cancer Survival by Ethnicity
Regional and Local Stage at Diagnosis

Regional Stage Disease



Log-rank test p < 0.02
Hispanic n = 163
NHW n = 195

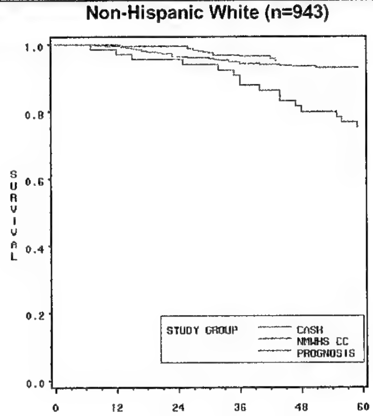
Local Stage Disease



Log-Rank test p < 0.98
Hispanic n = 286
NHW n = 561

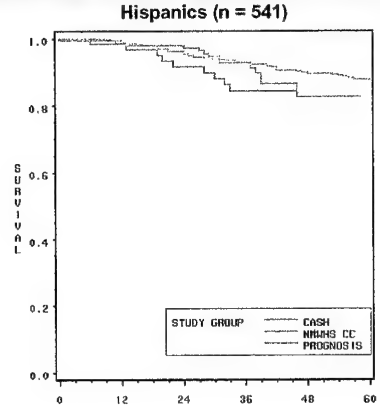
5 Yr. Breast Cancer Survival by Study Cohort

Non-Hispanic White (n=943)

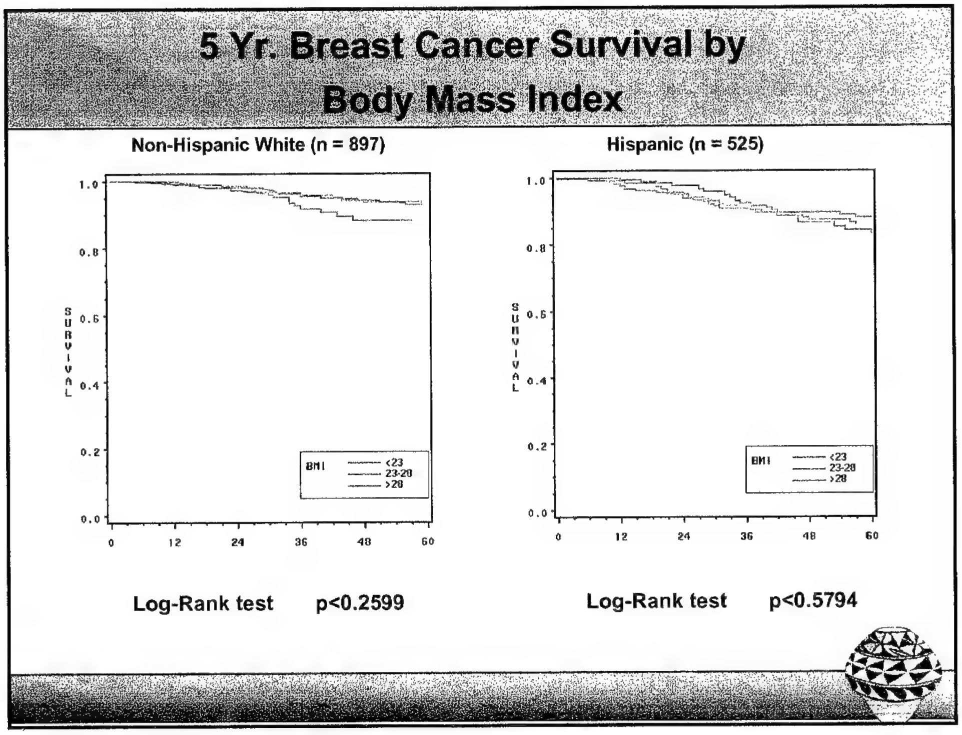


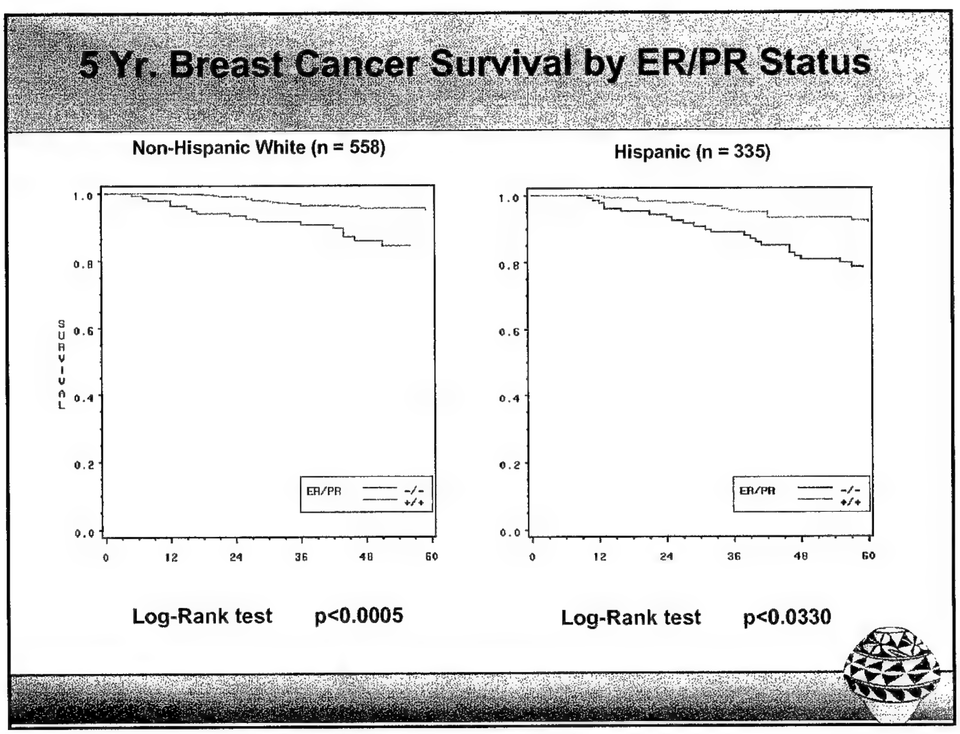
Log-Rank test p<0.0001

Hispanics (n = 541)



Log-Rank test p<0.0070


5 Yr. Breast Cancer Survival by Body Mass Index
Non-Hispanic White (n = 897)
Hispanic (n = 525)
SURVIVAL
BMI
<23
23-28
>28
Log-Rank test p<0.2599
Log-Rank test p<0.5794


5 Yr. Breast Cancer Survival by ER/PR Status
Non-Hispanic White (n = 558)
Hispanic (n = 335)
SURVIVAL
ER/PR
-/-
+/+
Log-Rank test p<0.0005
Log-Rank test p<0.0330

Part II

An examination of the association between body composition measures and prognostic factors Including:

- **negative estrogen receptor status (ER-)**
- **maximum tumor diameter**

Study cohort is NMWHS Prognosis cohort (1996-99) Including:

- **invasive cases only**
- **women with known values for both ER/PR and tumor size**
- **complete body composition measures**

Recurrence/Breast Cancer Death Prognosis Cohort

	No Recurrence		Recurrence and/or Death Breast Cancer		p-value
	N	%	N	%	
All:	446		35		
TNM stage					
0	88	19.7	3	8.6	0.0003
I	221	49.6	13	37.1	
IIA	98	22.0	8	22.9	
IIB	32	7.2	10	28.6	
IIIA IIIB	5	1.1	1	2.9	
Ethnic group					
non-Hispanic white	353	79.1	20	57.1	0.0023
Hispanic	93	20.9	15	42.9	
Estrogen-receptor status					
Not done/unknown	129	28.9	11	31.4	0.0078
Positive	256	57.4	14	40.0	
Negative/borderline	61	13.7	10	28.6	
Months since prior mammogram					
Unknown	18	4.0	2	5.7	0.0126
<=15	239	53.6	11	31.4	
>15	189	42.4	22	62.9	

Multiple Logistic Regression Model of ER- Status on Body Composition Measures*

	Hispanic (n=84)			NHW (n=269)		
	OR	95% CI	P-value	OR	95% CI	P-value
BMI (kg/m²)	1.08	(0.98, 1.18)	0.13	1.00	(0.95, 1.07)	0.91
Total body fat (kg)	**1.09**	(1.01, 1.19)	**0.04**	1.01	(1.00, 1.05)	0.51
Percent body fat	1.12	(0.99, 1.27)	0.06	1.02	(0.98, 1.07)	0.32
Triceps (cm)	**1.08**	(1.01, 1.15)	**0.02**	1.00	(0.96, 1.03)	0.97
Thigh circumference (cm)	**1.10**	(1.00, 1.21)	**0.05**	0.98	(0.92, 1.03)	0.39
Waist circumference (cm)	1.03	(0.98, 1.07)	0.25	0.99	(0.97, 1.02)	0.70

Negative estrogen receptor status is significantly associated with total body fat & measures of peripheral fat distribution among Hispanics.

*(Adjusted for menopausal status, family history, age at first birth, & mammography screening interval.)

Multiple Linear Regression Model of Tumor Size on Body Composition Measures*

	NHW (n=269)			Hispanic (n=84)		
	Slope	95% CI	P-value	Slope	95% CI	P-value
BMI (kg/m²)	**0.007**	(0.001, 0.013)	**0.03**	-0.008	(-0.016, 0.001)	0.09
Total body fat (kg)	0.003	(-0.001, 0.007)	0.13	-0.004	(-0.010, 0.003)	0.26
Triceps (cm)	0.004	(-0.001, 0.007)	0.06	-0.001	(-0.006, 0.006)	0.93
Subscapular (cm)	**0.003**	(0.001, 0.007)	**0.04**	0.002	(-0.003, 0.007)	0.53
Waistline (cm)	**0.003**	(0.001, 0.006)	**0.02**	-0.002	(-0.006, 0.002)	0.27
Waist/hip ratio	0.500	(-0.015, 1.01)	0.06	0.048	(-0.848, 0.943)	0.92

Log tumor size was positively associated with BMI & measures of centralized obesity among NHW women.

*(Adjusted for menopausal status, family history, age at first birth, & mammography screening interval.)

Results Summary

Hispanics have significantly higher "all cause" and breast cancer mortality.

When adjusted for stage of disease, breast cancer mortality was significantly higher for Hispanics with regional stage at diagnosis.

There were no ethnic differences in breast cancer mortality for local stage disease.

Results Summary

Breast cancer and "all cause" mortality was not significantly associated with BMI when the three study cohorts were combined.

"All cause" mortality was significantly greater among NHW women in the highest BMI category, in the CASH and in the NMWHS.

Within the Prognosis cohort, total body fat and peripheral measures were significantly associated with ER- status among Hispanic women.

ER- status was significantly associated with recurrence and/or breast cancer death.

Results Summary

Women diagnosed with ER-/PR- tumors experience significantly higher 5 year breast cancer mortality compared to cases with ER+/PR+ tumors.

The magnitude of this mortality difference was greater for Hispanics
(16% vs. 5% for NHW and 21% vs. 8% Hispanic).

Future research will investigate factors associated with the ethnic differences in the prevalence of ER-/PR- tumors.

American Journal of Epidemiology

Vol. 154, No. 5
Printed in U.S.A.

Physical Activity and Breast Cancer Risk in Hispanic and Non-Hispanic White Women

Frank D. Gilliland,[1,2] Yu-Fen Li,[1] Kathy Baumgartner,[2] Diane Crumley,[2] and Jonathan M. Samet[3]

To investigate breast cancer risk in Hispanic and non-Hispanic White women, the authors conducted a population-based case-control study of New Mexican women during 1992–1994 using incident breast cancer cases aged 35–74 years and frequency-matched controls selected using random digit dialing. Activity type and weekly duration of usual nonoccupational physical activity were used to calculate weekly metabolic equivalent (MET)-hours of total and vigorous physical activity (≥5 METs). Conditional logistic regression models were fitted to estimate the relative risk of breast cancer for levels of physical activity and to assess the difference in effects by ethnicity, body mass index, energy intake, and menopausal status. Vigorous physical activity was associated with reduced breast cancer risk in both Hispanic and non-Hispanic White women. Women in the highest category of vigorous activity had lower risk of breast cancer (adjusted odds ratio = 0.34, 95% confidence interval: 0.22, 0.51 for Hispanic; adjusted odds ratio = 0.60, 95% confidence interval: 0.41, 0.89 for non-Hispanic White women) compared with women reporting no vigorous physical activity. Both pre- and postmenopausal Hispanic women showed decreasing risk with increasing level of activity. Physical activity was protective only among postmenopausal non-Hispanic White women. The effects of physical activity were independent from reproductive factors, usual body mass index, body mass index at age 18, adult weight gain, and total energy intake. *Am J Epidemiol* 2001;154:442–50.

body mass index; breast neoplasms; energy intake; exercise; Hispanic Americans

The Hispanic population in the United States is currently estimated to exceed 20 million by the year 2030 and is projected to become the largest minority population (1). Breast cancer is the most common cancer among Hispanic women and a leading cause of cancer mortality (2–5). Moreover, both incidence and mortality rates are increasing at an alarming pace among Hispanic women (3, 4). Yet while published studies on the risk factors for breast cancer are extensive for non-Hispanic women in the United States and other countries, little information is available for Hispanic women (5–13).

Differences in reproductive patterns were thought to underlie the ethnic variation and rising cancer incidence rates among Hispanic women; however, we have shown that reproductive risk factors, such as age at first full-term birth, parity, and breastfeeding, account for only a small portion of the ethnic differences in risk or temporal trends (8). Results from studies of other established risk factors, such as a family history of breast cancer and body mass index, have been inconsistent (5–13). Because reproductive factors do not account for the differences in breast cancer occurrence between Hispanic and non-Hispanic White women, the contribution of other potential determinants of breast cancer risk, especially modifiable lifestyle factors, is of interest.

A growing body of evidence indicates that women who are the most physically active have substantially reduced breast cancer risk, especially women who participate in vigorous physical activities (14–17). Studies of the relation between physical activity and breast cancer risk have largely included non-Hispanic White women, resulting in a paucity of data about the effects of physical activity on breast cancer risk among Hispanic and other ethnic minority women (18).

To investigate the relations of physical activity with breast cancer risk in Hispanic and non-Hispanic White women, we examined data collected in the New Mexico Women's Health Study, a statewide population-based case-control study. We assessed the associations of usual level of nonoccupational physical activity, adjusted for selected aspects of reproductive history, usual energy intake, and body mass index, with breast cancer risk in pre- and postmenopausal Hispanic and non-Hispanic White women aged 30–74 years.

Received for publication August 30, 2000, and accepted for publication February 14, 2001.

Abbreviation: MET, metabolic equivalent.

[1] Division of Occupational and Environmental Health, Department of Preventive Medicine, and Norris Comprehensive Cancer Center, University of Southern California Health Sciences Center, Los Angeles, CA.
[2] New Mexico Tumor Registry, Cancer Research and Treatment Center, University of New Mexico Health Sciences Center, Albuquerque, NM.
[3] Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.
Reprint requests to Dr. Frank Gilliland, USC Keck School of Medicine, 540 Alcazar, #236, Los Angeles, CA 90033 (e-mail: gillilan@usc.edu).

TABLE 1. Distribution for selected demographic characteristics and breast cancer risk factors among cases and controls, New Mexico Women's Health Study, 1992–1994*

Risk factor	Hispanic			Non-Hispanic		
	Cases (*n* = 332) (%)	Controls (*n* = 388) (%)	*p* value†	Cases (*n* = 380) (%)	Controls (*n* = 456) (%)	*p* value
Education (years)						
<12	31.5	22.2		6.3	6.4	
12	39.4	38.7	0.004	26.9	24.4	0.705
>12	29.1	39.2		66.8	69.2	
Age (years) at menarche						
≤12	40.4	43.9		48.7	46.5	
13	30.7	28.2	0.618	29.2	30.8	0.808
≥14	28.9	27.9		22.1	22.7	
Age (years) at first full-term birth						
≤18	21.4	22.9		11.3	14.7	
19–20	21.4	24.2		15.8	16.0	
21–22	15.1	16.5	0.557	15.5	14.0	0.784
23–26	18.7	17.5		21.6	20.8	
≥27	12.0	11.1		20.0	18.4	
Nulliparous	11.4	7.7		15.8	16.0	
No. of full-term births						
Nulliparous	11.4	7.7		15.8	16.0	
1	8.7	9.0		16.6	12.7	
2	19.9	25.3	0.088	33.7	30.3	0.208
3	24.1	18.6		17.4	22.1	
≥4	35.8	39.4		16.6	18.9	
Cumulative months of lactation						
Nulliparous	11.4	7.8		15.8	16.0	
Parous, 1–12	40.1	37.7	0.121	28.9	27.4	0.001
Parous, >12	32.8	33.2		43.9	34.9	
Parous, never	15.7	21.3		11.3	21.7	
Cumulative years of oral contraceptive use						
Never	45.3	37.7		40.2	34.1	
<1.5	18.8	21.4		23.1	16.5	
1.5–<6	15.5	19.9	0.286	17.4	24.0	0.010
6–<10	9.7	10.1		9.4	12.3	
≥10	10.6	10.9		9.9	13.0	

Table continues

did not vary significantly across levels of usual body mass index, body mass index at age 18, weight gain, energy intake, or parity (data not shown).

DISCUSSION

The relation between a woman's risk of breast cancer and physical activity has been the subject of a growing number of investigations (15, 17). Our results support the hypothesis that high levels of physical activity reduce breast cancer risk in both Hispanic and non-Hispanic White women. The protective effects of physical activity in both ethnic groups are consistent with the evolving consensus that high energy expenditure during leisure time physical activity is associated with an approximate 30 percent reduction in breast cancer risk (15, 17).

In our study population, Hispanic women showed a stronger protective effect of nonoccupational physical activity than did non-Hispanic White women. More than 30 studies of physical activity and breast cancer risk have been reported, but few studies have investigated the effects of physical activity on breast cancer risk among women from diverse racial and ethnic groups, and, to our knowledge, none has investigated the effects of physical activity among Hispanic women (15, 18). Our findings suggest that physical activity may be an important protective behavior among Hispanic women and that more targeted research is warranted to investigate the effects of physical activity in other Hispanic populations.

MATERIALS AND METHODS

The New Mexico Women's Health Study is a statewide population-based case-control study of breast cancer in Hispanic and non-Hispanic White women. Results from this study have been reported previously for reproductive breast cancer risk factors (8). Women newly diagnosed with an invasive or in situ breast carcinoma during the period from January 1, 1992, through December 31, 1994, who were residents of the state and aged between 30 and 74 years at diagnosis were eligible for the study.

Identification of case subjects

Women with new primary breast cancer were ascertained by the New Mexico Tumor Registry, a population-based tumor registry and a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (19). All Hispanic cases were eligible for the study. Because the overall expected number of breast cancer cases for the study period was approximately three times higher for non-Hispanic Whites than for Hispanics, we randomly selected approximately 33 percent of non-Hispanic White cases while including all Hispanic cases to maximize our power to examine ethnic differences in risk with the available sample size and funding. The sampling strata for non-Hispanic White cases were age group (30–39, 40–64, 65–74 years) and geographic region defined by seven state health-planning districts. The sampling fraction for non-Hispanic Whites in each of these 21 strata was chosen to give a distribution similar to the age and geographic distribution of Hispanic cases ascertained by the New Mexico Tumor Registry in the 3-year period 1988 through 1990. A total of 491 eligible Hispanic breast cancer cases were ascertained. The stratified random selection of non-Hispanic White women resulted in ascertainment of 493 cases. Of the eligible cases, 332 Hispanics, 68 percent, and 380 non-Hispanic Whites, 77 percent, completed interviews. Reasons for non-participation have been reported elsewhere (8).

Identification of controls

Controls were ascertained using random digit dialing with frequency matching on ethnicity, the three age groups, and the seven health-planning districts. We used a modified approach to the Waksberg (20) random digit dialing method that has been described previously (8). There were a total of 1,039 eligible controls ascertained from approximately 3,400 respondents who completed the telephone-screening interview including 511 Hispanic and 528 non-Hispanic White women. Of those eligible, 844 (81.2 percent) were successfully interviewed. Participation rates were 75.9 percent for Hispanics and 86.4 percent for non-Hispanic Whites.

Data collection

In-person interviews were conducted at a location of the participant's choice. Written informed consent was obtained at the onset of the interview. The median time between diagnosis and interview was 193 days. To aid in recall, interviewers used a calendar that recorded major life events. Only events that occurred before each woman's reference date were recorded (date of diagnosis for cases and date of interview for controls). All questionnaires were translated into Spanish, and interviews were conducted in Spanish or English according to the participant's preference.

Physical activity, body mass index, and energy intake

Self-reported categories of nonoccupational physical activity were assessed during the in-person interview. Participants were asked to indicate activities that they had done on a regular basis (for at least 6 months) during the year prior to the reference date and the amount of time per week (<1, 1.5, 2–3, 4–6, 7–10, ≥11 hours) spent doing each activity. Activities included walking/hiking, running/jogging, exercise class, biking, dancing, lap swimming, tennis, squash/racquetball, calisthenics/rowing, bowling, golf, softball/baseball, basketball, volleyball, housework, and heavy outside work.

For each participant, we computed weekly average energy expenditure by assigning metabolic equivalents (METs) in kcal/kg/hour to each activity and multiplying by the midpoint of the hours per week categories to obtain MET-hours/week (21). MET-hours were used to rank women's total energy expenditure for all nonoccupational physical activity and for energy expended during vigorous physical activities. Vigorous activities were defined as activities associated with ≥5 METs. Usual adult body mass index was calculated using self-reported usual adult weight and height (weight (kg)/height (m)^2).

Dietary intake was collected using a modified version of a quantitative food frequency questionnaire that was validated in our study population and has been previously used in other Hispanic populations (22, 23). The food frequency questionnaire included unique food items that were important sources of nutrients among New Mexico women. Participants were asked to recall usual food intake during a 4-week period approximately 6 months prior to the reference date. Frequency of consumption and portion size were used to calculate total energy and nutrient intake per day using a database developed by the Human Nutrition Center at the University of Texas-Houston (24).

Covariates

Parity was defined as the number of pregnancies lasting 6 months or longer with outcomes of either a single birth, multiple births, or a stillbirth. Age at first full-term birth was defined as the age of the woman at the end of her first pregnancy lasting 6 months or longer, regardless of the outcome of the pregnancy. Duration of lactation was the cumulative number of months of breastfeeding for all children. Menstrual history, history of hysterectomy with or without oophorectomy, and use of estrogen replacement therapy were used to determine menopausal status as previously described (8). The categories of menopausal status used in this analysis include premenopausal, postmenopausal, and

unknown. The cumulative number of years of oral contraceptive use and hormone replacement therapy was collected using a life events calendar. Hormone replacement therapy included cumulative number of years of estrogen or estrogen plus progesterone use. Family history of breast cancer was coded as positive if the respondent reported a first-degree relative, mother, sister, or daughter, with breast cancer. History of fibrocystic disease (yes/no) was defined as having been diagnosed with fibrocystic breast disease.

Statistical analysis

Conditional logistic regression, which conditioned on the frequency-matched variables (three age groups, geographic district, and ethnicity), was used to compute odds ratios and 95 percent confidence intervals. Multivariate odds ratios from conditional logistic regression were used to estimate the joint effects of physical activity, energy intake, and body mass index adjusted for reproductive and nonreproductive factors (25). We selected potential confounding variables based on review of the literature, univariate analyses, and change of the effect estimates by 10 percent or more in multivariate analyses. To assess differences in risk for Hispanics and non-Hispanic Whites, analyses were stratified by ethnicity with models conditioned on age groups and geographic districts. An overall test of equality of effects for Hispanics and non-Hispanic Whites was conducted by comparing models using the likelihood ratio test. Tests of trend were computed using the median values within each category of activity level. Modification of the effects of physical activity, body mass index, and energy intake by ethnicity or the other factors was investigated using stratified models and tested by comparing appropriate likelihood ratio statistics in nested models that included interaction terms. Stratified models were fitted to assess differences in effects between pre- and postmenopausal women. Women with unknown menopausal status were excluded from the stratified analyses (n = 4). All analyses were performed using Statistical Analysis System software (26).

RESULTS

Distributions of the selected demographic characteristics of cases and controls are presented in table 1. Hispanic women with breast cancer were less educated, used hormone replacement therapy less often, and had lower parity than did Hispanic controls (table 1). Non-Hispanic White cases had a shorter duration of oral contraceptive use, a stronger family history of breast cancer, lower fat intake, and more fibrocystic breast disease than did non-Hispanic White controls. In general, Hispanic women had less education, had an earlier age at first full-term birth, had a higher parity, used less hormone replacement therapy, had less fibrocystic breast disease, and had fewer first-degree relatives with breast cancer compared with non-Hispanic White women. Fat intake was higher among Hispanic than non-Hispanic White women (96 vs. 90 g/day, p = 0.01). Hispanic participants were estimated to have a higher daily energy intake than non-Hispanic White participants (2,484 vs. 2,281 kcal/day, p < 0.001), respectively. Energy intake varied between cases and controls (table 1). Among non-Hispanic White women, cases reported lower energy intake than did controls. Among Hispanic cases and controls, energy intake showed no consistent differences. Hispanic participants had a higher body mass index than did non-Hispanic White participants (table 1). At the reference date, the mean age of cases was 54 years (age at diagnosis) and was 53 years for controls. As expected from the frequency-matched design, the age distribution for cases and controls was not statistically different between Hispanic or non-Hispanic White participants. Approximately one third of the women were premenopausal.

Among both Hispanic and non-Hispanic White participants, the five most commonly reported nonoccupational activities were housework, walking, heavy outside work, biking, and dancing. Hispanic women reported a greater number of activities (mean number of activities = 8.6) and total weekly hours of activity (mean = 13.4 hours) than did non-Hispanic White women (mean number of activities = 7.1, mean = 12.4 hours).

Total and vigorous MET-hours for nonoccupational physical activity were lower in both Hispanic and non-Hispanic White cases than in their respective controls (table 2). Cases were more likely than controls to report no vigorous activities and less likely to expend more than 25 MET-hours/week in vigorous activity. Differences in total physical activity levels followed the same pattern as vigorous physical activity levels, but they were less pronounced among Hispanic women.

High levels of vigorous physical activity were associated with substantial reductions in breast cancer risk in Hispanic and non-Hispanic White women (table 3). Among women who expended 25 or more MET-hours/week performing vigorous activity, Hispanic women had a 66 percent decrease in risk compared with a 40 percent decrease for non-Hispanic White women who performed no vigorous activity. Furthermore, increasing amounts of vigorous activity were associated with greater reductions in risk. Total physical activity levels were also associated with reduced risk for breast cancer, except among non-Hispanic White women who showed no clear evidence of a reduction in risk.

The larger protective effect of physical activity among Hispanic than non-Hispanic White women resulted primarily from ethnic differences in the protective effect among premenopausal women (table 3). Hispanic women who were premenopausal had substantial reductions in the risk of breast cancer associated with increasing MET-hours/week of both vigorous activities and total activity, and the effects were larger than among non-Hispanic White women. Risk among premenopausal non-Hispanic White women was not associated with activity levels. Among postmenopausal women, high levels of total and vigorous activity were associated with an approximate 50 percent reduction in risk in both ethnic groups. Further adjustments for family history of breast cancer, history of fibrocystic disease, education, body mass index at age 18, weight change, and dietary fat intake did not result in substantial changes in any of the effect estimates for physical activity. The effects of physical activity

TABLE 1. Continued

Risk factor	Hispanic Cases (n = 332) (%)	Hispanic Controls (n = 388) (%)	Hispanic p value	Non-Hispanic Cases (n = 380) (%)	Non-Hispanic Controls (n = 456) (%)	Non-Hispanic p value
Menopausal status‡						
Premenopausal	39.5	39.7		30.5	40.8	
Postmenopausal	53.6	56.4	0.179	62.9	54.6	0.007
Unknown	6.9	3.9		6.6	4.6	
Estrogen use (years)						
Never	66.9	58.1		47.5	53.5	
≤1	12.5	17.3		11.9	11.9	
>1–≤4	6.7	5.4	0.038	11.4	10.6	0.340
>4–≤10	6.1	10.9		13.0	9.3	
>10	7.9	8.3		16.2	14.8	
History of fibrocystic disease						
No	86.4	89.7	0.179	75.0	83.1	0.004
Yes	13.6	10.3		25.0	16.9	
Breast cancer in mother, sister, and daughter						
No	88.0	90.7	0.228	83.4	88.2	0.049
Yes	12.0	9.3		16.6	11.8	
Cigarette smoking						
No	83.4	88.2	0.253	51.3	47.4	0.256
Yes	16.6	11.8		48.7	52.6	
Total fat intake (g/day)						
<50	14.6	12.4		17.5	12.1	
50–<75	28.0	25.7		34.2	30.1	
75–<100	23.7	21.7	0.282	21.0	24.2	0.043
100–<125	13.1	19.3		13.5	14.5	
≥125	20.7	20.9		13.8	19.1	
Energy intake (kcal/day)						
<1,600	20.1	22.1		26.3	17.1	
1,600–<2,000	17.6	14.2		23.6	23.1	
2,000–<2,400	20.7	17.3	0.428	17.5	19.8	0.020
2,400–<3,000	17.9	20.9		16.7	20.2	
≥3,000	23.7	25.5		15.9	19.8	
Usual body mass index (kg/m²)						
<22	27.2	21.0		44.3	50.5	
22–<25	34.8	34.7	0.091	33.9	28.8	0.301
25–<30	27.5	28.9		15.4	15.1	
≥30	10.5	15.5		6.4	5.6	

* Numbers may not sum to total for all covariates because of missing data.
† p value from chi-square tests.
‡ Premenopausal includes premenopausal and surgical unknown (age, <44 years); postmenopausal includes post-natural menopause, surgical menopause, and surgical unknown (age, ≥54 years).

The findings of studies that examined physical activity among postmenopausal women have shown heterogeneous results that ranged from a significant decrease in risk to no association and an increase in risk (15, 18). In the present study, the substantial protective effects of high levels of energy expenditure were apparent in both Hispanic and non-Hispanic White postmenopausal women and indicate that recent activity levels may contribute to reduced risk in postmenopausal women. Because recent activity is likely to be correlated with past activity levels, it is difficult to clearly determine if this protective effect is due to recent activity or to a cumulative lifetime effect.

The effects of physical activity in younger and premenopausal women, in general, have been found to be somewhat more consistent and to have a larger protective effect of physical activity than in postmenopausal women

TABLE 2. Distribution of total and vigorous physical activity (MET*-hours/week) for Hispanic and non-Hispanic White participants, New Mexico Women's Health Study, 1992–1994

Risk factor	Hispanic		Non-Hispanic	
	Cases (n = 332) (%)	Controls (n = 388) (%)	Cases (n = 380) (%)	Controls (n = 456) (%)
Total physical activity (MET-hours/week)†				
0–<25	30.2	16.3	26.2	21.1
25–<50	35.1	29.5	29.1	30.3
50–<80	19.6	27.9	27.2	27.3
≥80	15.1	26.3	17.5	21.3
Vigorous physical activity (MET-hours/week)‡				
0	44.4	27.1	28.0	18.9
1–<25	35.4	36.7	36.8	40.7
≥25	20.2	36.2	35.2	40.4

* MET, metabolic equivalent, based on expenditure of kcal/kg of weight/hour. Physical activities included walking/hiking, running/jogging, exercise class, biking, dancing, lap swimming, tennis, squash/racquetball, calisthenics/rowing, bowling, golf, softball/baseball, basketball, volleyball, housework, and heavy outside work.

† The median total physical activity (MET-hours/week) is 42.00, 51.75, 42.50, and 48.25 for Hispanic cases, Hispanic controls, non-Hispanic cases, and non-Hispanic controls, respectively.

‡ The median vigorous physical activity (MET-hours/week) is 2.5, 12.5, 12.5, and 12.5 for Hispanic cases, Hispanic controls, non-Hispanic cases, and non-Hispanic controls, respectively.

(14, 15, 18). We found that the effects of physical activity were larger among premenopausal Hispanic than non-Hispanic White women. The heterogeneity among premenopausal women suggests that it may be important to examine the effects of physical activity within ethnic groups and menopausal status.

The interpretation of the evidence for a protective effect of physical activity is complex because levels of physical activity are interrelated with other physiologic risk factors including energy intake and obesity (15, 18). Substantial variation in the effects of physical activity has been reported for lean and nonlean women, suggesting that energy intake and body mass may modify or confound the effects of physical activity (15, 18, 27, 28). If energy balance is important in breast carcinogenesis, then consideration of the simultaneous effects of physical activity, body mass index, and energy intake may be important for clarifying the relation of physical activity with breast cancer, as well as the underlying mechanism for its inverse association with breast cancer risk. In our study, variation in body mass index at age 18, usual adult body mass index, or current body mass index, as well as adult weight gain, and energy intake did not account for the strong protective effects of physical activity, suggesting that high levels of physical activity do not primarily act through effects on obesity or energy intake. Furthermore, the effects of physical activity did not vary substantially when stratified by body mass index or adult weight gain, indicating that the protective effects of recent activity occur for lean and obese women and are unaffected by weight gain. Based on these results, we conclude that the association of physical activity with breast cancer risk is independent of body mass index and energy intake.

The mechanisms for the protective effects of physical activity have yet to be clarified. Potential etiologic mechanisms include changes in fat distribution, alterations in reproductive function and sex hormone levels, metabolic and growth hormones, and modulation of immune function (15, 17, 18). In addition, the protective effects of physical activity may be mediated directly through effects on ovarian and peptide hormone production in premenopausal women (29–31). A leading candidate mechanism is that high levels of physical activity result in a preferential reduction of intraabdominal fat stores that leads to lower exposure to estrogens and other hormonal breast epithelial cell mitogens, such as insulin-like growth factor 1 and insulin (15, 17, 18). Because Hispanic women have a higher prevalence of obesity and relatively greater intraabdominal fat than do non-Hispanic White women, the effects of physical activity may be larger among Hispanics. We were unable to investigate this hypothesis because we lack data on the relevant component of body fat.

A number of limitations affect interpretation of our results. Response rates were reasonably high for both Hispanic and non-Hispanic subjects, indicating that a large selection bias is unlikely, but a potential bias may have arisen from our sampling scheme for control subjects. Control subjects were selected by random digit dialing methods that may introduce differences between cases and controls because telephone coverage varies by socioeconomic variables and other health-related factors in New Mexico (32). To reduce this possibility, we selected controls from strata defined by age, ethnicity, and geographic region to ensure a distribution similar to that of the cases. Assessment of energy intake using self-report has recognized limitations (33). The accuracy of self-report varies by respondent body mass index, with greater error at the extremes of the distribution. To assess the effects of this misreporting, we restricted our analyses to women with a body mass index between 20 and 25 and found that the estimates for physical activity showed the same patterns in the restricted sample as for the overall study.

TABLE 3. Effects of physical activity on breast cancer risk in premenopausal and postmenopausal Hispanic and non-Hispanic White women, adjusted odds ratios* and 95% confidence intervals, New Mexico Women's Health Study, 1992–1994

Risk factor	All women				Premenopausal women				Postmenopausal women			
	Hispanic		Non-Hispanic		Hispanic		Non-Hispanic		Hispanic		Non-Hispanic	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Total physical activity (MET†-hours/week)												
0–<25	1.00		1.00		1.00		1.00		1.00		1.00	
25–<50	0.69	0.44, 1.06	0.74	0.49, 1.11	1.17	0.53, 2.55	1.35	0.64, 2.85	0.74	0.40, 1.36	0.45	0.26, 0.78
50–<80	0.34	0.21, 0.55	0.79	0.52, 1.20	0.49	0.22, 1.07	1.44	0.67, 3.10	0.37	0.18, 0.75	0.49	0.28, 0.86
≥80	0.30	0.18, 0.49	0.67	0.43, 1.06	0.29	0.12, 0.72	1.13	0.49, 2.61	0.38	0.18, 0.77	0.45	0.24, 0.85
Trend test	$p < 0.001$		$p = 0.129$		$p < 0.001$		$p = 0.741$		$p = 0.002$		$p = 0.019$	
Interaction with ethnicity	$p = 0.016$				$p = 0.049$				$p = 0.320$			
Vigorous physical activity (MET-hours/week)												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1–<25	0.60	0.41, 0.87	0.65	0.44, 0.96	0.50	0.26, 0.97	0.68	0.32, 1.42	0.65	0.38, 1.10	0.58	0.35, 0.97
≥25	0.34	0.22, 0.51	0.60	0.41, 0.89	0.17	0.08, 0.36	0.85	0.40, 1.79	0.52	0.29, 0.93	0.50	0.30, 0.84
Trend test	$p < 0.001$		$p = 0.014$		$p < 0.001$		$p = 0.834$		$p = 0.028$		$p = 0.010$	
Interaction with ethnicity	$p = 0.066$				$p = 0.002$				$p = 0.907$			

* Conditional logistic regression models with strata for age group and health planning district. Adjusted covariates: all (319 cases and 376 controls in Hispanic women; 365 cases and 447 controls in non-Hispanic women)—age within strata, age at first full-term birth, months of lactation, parity, years of oral contraceptive use, and menopausal status; premenopausal (128 cases and 152 controls in Hispanic women; 115 cases and 183 controls in non-Hispanic women)—age within strata, age at first full-term birth, months of lactation, parity, years of oral contraceptive use; postmenopausal (171 cases and 210 controls in Hispanic women; 228 cases and 224 controls in non-Hispanic women)—age within strata, age at first full-term birth, months of lactation, parity, years of oral contraceptive use, and years of hormone replacement therapy use.

† OR, odds ratio; CI, confidence interval; MET, metabolic equivalent.

Assessment of physical activity is difficult, and a standardized approach has yet to be developed for use in epidemiologic studies. Accordingly, studies of the relation of physical activity and breast cancer have used a variety of methods to assess usual patterns of physical activity. These methods differ in the type of physical activity (leisure, nonoccupational, occupational), period of assessment (lifetime, age periods, recent), and the specificity of parameters needed to estimate energy expenditure (activity, frequency, duration, and intensity) (14, 16, 28, 34, 35). All the methods are likely to result in some degree of misclassification of participants' activity levels (36). We assessed the type and duration of usual nonoccupational time physical activity performed regularly on a weekly basis during a 1-year time period, the year prior to the reference date. We chose to include both leisure time activities and nonoccupational activities (housework and heavy outside), because this provides a more complete assessment of energy expenditure outside of paid employment in our study population. We lack data to directly assess the validity or reliability of our assessment of physical activity in our study population, but the use of a 1-year period is likely to misclassify some participants, especially if lifetime levels of activity or activity during specific life stages is the biologically relevant exposure period. Furthermore, we did not include occupational activities that may be more important in rural and minority populations (37–39). Selecting cases and controls within geographic strata with relatively homogeneous population densities and industries minimized the potential for differential bias. Such misclassification or misspecification of the relevant time period likely would be the same for cases and controls, thus reducing the magnitude of protective effects we observed. The use of recent activity levels is supported by findings in some, but not all, studies that show recent physical activity is associated with decreased breast cancer risk (14, 28). Although differential misclassification among cases and controls is possible, recall of physical activity was unlikely to be substantially different in cases and controls in this study because participants were interviewed in the early 1990s before physical activity received a great deal of media attention as a protective factor for breast cancer (15, 40). It is also possible that reporting of prediagnosis physical activity may be affected by treatment among cases. Women who are less active because of poor well-being from active breast cancer treatment might underreport physical activity in the year prior to diagnosis. This would tend to overestimate the effect of physical activity in a case-control design. However, we are not aware of studies that show how current levels of activity after the diagnosis of breast cancer affect the validity of recall about prediagnosis activity levels. We also examined the sensitivity of our findings to changes in our definitions of physical activity metrics. We redefined vigorous activity as activities with greater than or equal to 6 METs and found that the effects in Hispanic women were robust but were no longer significant among non-Hispanic White women. We also conducted analyses using physical activity metrics that excluded housework and outside work and found that the effect estimates were reduced in magnitude and no longer significant for non-Hispanic White women for both total and vigorous activity.

Our findings have public health significance. The proportion of Hispanic women who live sedentary lifestyles is high and rising (39, 41). Because Hispanic women appear to be at greater risk for breast cancer from low levels of physical activity than are non-Hispanic Whites, the increasing prevalence of sedentary lifestyles may presage a disproportionate increase in breast cancer occurrence among this growing ethnic population. Interventions are needed to reverse the trends toward increasingly sedentary lifestyles not only to prevent breast cancer but also to reduce the other increasing burdens of diabetes and cardiovascular disease.

In conclusion, Hispanic and non-Hispanic women with high levels of physical activity during nonoccupational physical activity were at substantially reduced risk of breast cancer. The overall protective effects of physical activity were larger in Hispanic than non-Hispanic White women as a result of a protective effect among premenopausal Hispanic women that was not apparent among premenopausal non-Hispanic White women.

ACKNOWLEDGMENTS

This research was supported by grant R01-CA55730 from the National Cancer Institute and by the Norris Comprehensive Cancer Center, University of Southern California Health Sciences Center.

REFERENCES

1. Ramirez AG, Villarreal R, Suarez L, et al. The emerging Hispanic population: a foundation for cancer prevention and control. J Natl Cancer Inst Monogr 1995;(18):1–9.
2. Miller B, Kolonel L, Bernstein L. Racial/ethnic patterns of cancer in the United States 1988–1992. Bethesda, MD: National Cancer Institute, 1996.
3. Becker T, Wiggins C, Elliott R, et al. Racial and ethnic patterns of mortality in New Mexico. Albuquerque, NM: University of New Mexico Press, 1993.
4. Eidson M, Becker TM, Wiggins CL, et al. Breast cancer among Hispanics, American Indians, and non-Hispanic whites in New Mexico. Int J Epidemiol 1994;23:231–7.
5. Trapido EJ, Burciaga Valdez R, Obeso JL, et al. Epidemiology of cancer among Hispanics in the United States. J Natl Cancer Inst Monogr 1995;(18):17–28.
6. Bondy ML, Spitz MR, Halabi S, et al. Low incidence of familial breast cancer among Hispanic women. Cancer Causes Control 1992;3:377–82.
7. Buchanan AV, Weiss KM, Anderson DE, et al. Epidemiology of breast cancer in a Mexican-American population. J Natl Cancer Inst 1985;74:1199–206.
8. Gilliland FD, Hunt WC, Baumgartner KB, et al. Reproductive risk factors for breast cancer in Hispanic and non-Hispanic White women: the New Mexico Women's Health Study. Am J Epidemiol 1998;148:683–92.
9. Weiss KM, Chakraborty R, Smouse PE, et al. Familial aggregation of cancer in Laredo, Texas: a generally low-risk Mexican-American population. Genet Epidemiol 1986;3:121–43.
10. Mayberry RM, Branch PT. Breast cancer risk factors among Hispanic women. Ethn Dis 1994;4:41–6.
11. Longnecker MP, Paganini-Hill A, Ross RK. Lifetime alcohol

consumption and breast cancer risk among postmenopausal women in Los Angeles. Cancer Epidemiol Biomarkers Prev 1995;4:721–5.
12. Romieu I, Hernandez-Avila M, Lazcano E, et al. Breast cancer and lactation history in Mexican women. Am J Epidemiol 1996;143:543–52.
13. Calderon-Garciduenas AL, Paras-Barrientos FU, Cardenas-Ibarra L, et al. Risk factors of breast cancer in Mexican women. Salud Publica Mex 2000;42:26–33.
14. Verloop J, Rookus MA, van der Kooy K, et al. Physical activity and breast cancer risk in women aged 20–54 years. J Natl Cancer Inst 2000;92:128–35.
15. Gammon MD, John EM, Britton JA. Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst 1998;90:100–17.
16. Friedenreich CM, Rohan TE. A review of physical activity and breast cancer. Epidemiology 1995;6:311–17.
17. McTiernan A, Ulrich C, Slate S, et al. Physical activity and cancer etiology: associations and mechanisms. Cancer Causes Control 1998;9:487–509.
18. McTiernan A. Associations between energy balance and body mass index and risk of breast carcinoma in women from diverse racial and ethnic backgrounds in the U.S. Cancer 2000; 88:1248–55.
19. Hankey B, Ries L, Edwards B. The Surveillance, Epidemiology, and End Results Program: a national reference. Cancer Epidemiol Biomarkers Prev 1999;8:1117–21.
20. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
21. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71–80.
22. Baumgartner KB, Gilliland FD, Nicholson CS, et al. Validity and reproducibility of a food frequency questionnaire among Hispanic and non-Hispanic white women in New Mexico. Ethn Dis 1998;8:81–92.
23. McPherson RS, Kohl HW 3rd, Garcia G, et al. Food-frequency questionnaire validation among Mexican-Americans: Starr County, Texas. Ann Epidemiol 1995;5:378–85.
24. University of Texas-Houston School of Public Health. Food Frequency Data Entry and Analysis Program. Houston, TX: University of Texas-Houston Health Science Center, 1991.
25. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publication no. 32).
26. SAS Institute, Inc. SAS/STAT software: changes and enhancements through release 6.11. Cary, NC: SAS Institute, Inc, 1996.
27. Thune I, Brenn T, Lund E, et al. Physical activity and the risk of breast cancer. N Engl J Med 1997;336:1269–75.
28. Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–8.
29. Bernstein L, Ross RK, Lobo RA, et al. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. Br J Cancer 1987;55:681–5.
30. Bullen BA, Skrinar GS, Beitins IZ, et al. Induction of menstrual disorders by strenuous exercise in untrained women. N Engl J Med 1985;312:1349–53.
31. Broocks A, Pirke KM, Schweiger U, et al. Cyclic ovarian function in recreational athletes. J Appl Physiol 1990;68:2083–6.
32. Gilliland F, Mahler R, Davis S. Non-ceremonial tobacco use among southwestern rural American Indians: the New Mexico American Indian Behavioral Risk Factor Survey. Tob Control 1998;7:156–60.
33. Willett W. Nutritional epidemiology. New York, NY: Oxford University Press, 1990.
34. Gammon MD, Schoenberg JB, Britton JA, et al. Recreational physical activity and breast cancer risk among women under age 45 years. Am J Epidemiol 1998;147:273–80.
35. Friedenreich CM, Thune I, Brinton LA, et al. Epidemiologic issues related to the association between physical activity and breast cancer. Cancer 1998;83:600–10.
36. Ainsworth BE, Sternfeld B, Slattery ML, et al. Physical activity and breast cancer: evaluation of physical activity assessment methods. Cancer 1998;83:611–20.
37. Mayer EJ, Alderman BW, Regensteiner JG, et al. Physical-activity-assessment measures compared in a biethnic rural population: the San Luis Valley Diabetes Study. Am J Clin Nutr 1991;53:812–20.
38. Rauh MJ, Hovell MF, Hofstetter CR, et al. Reliability and validity of self-reported physical activity in Latinos. Int J Epidemiol 1992;21:966–71.
39. Brownson RC, Eyler AA, King AC, et al. Patterns and correlates of physical activity among US women 40 years and older. Am J Public Health 2000;90:264–70.
40. Falkner KL, Trevisan M, McCann SE. Reliability of recall of physical activity in the distant past. Am J Epidemiol 1999;150: 195–205.
41. Crespo CJ, Smit E, Andersen RE, et al. Race/ethnicity, social class and their relation to physical inactivity during leisure time: results from the Third National Health and Nutrition Examination Survey, 1988–1994. Am J Prev Med 2000;18: 46–53.